Viral Diseases Panels

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Guidelines

Viral Diseases Panels

High-priority research areas of the Viral Diseases Panels include the following:

Viruses that have arthropod vectors, particularly the flaviviruses, which cause diseases such as Japanese encephalitis and dengue

Viruses associated with intestinal infections, particularly viruses that cause gastroenteritis (e.g., rotaviruses, caliciviruses, and astroviruses)

Zoonotic viruses that have significant disease potential in humans and use wildlife as natural reservoirs or vectors, such as rabies virus; Hantaviruses and arenaviruses, both of which cause pulmonary syndrome or hemorrhagic fever; and Nipah virus

Viruses that are emerging, reemerging, or changing in their natural cycle or disease patterns

New research advances or technologies that might affect viral diseases

Five-Year Summary

Broad Goals

The Viral Diseases Panels consider viruses that cause significant morbidity and mortality in humans, with emphasis on viruses that are endemic or epidemic in the Americas and Asia. The Panels address general aspects of the epidemiology and geographic distribution of the agent, its clinical course and pathogenesis, and broad features of viral replication. Because the overarching goal is to advance scientific and public health methods to control these viruses, development of successful vaccines and antiviral drugs is a high priority for each of the Panels. In addition to research on well-studied viruses that continue to be significant human pathogens, the Viral Diseases Panels have, for many years, included research on emerging diseases and diseases that are reemerging with an expanded range.

Progress and Accomplishments

The range of dengue viruses continues to increase dramatically, and the Panels have devoted considerable effort to elucidating the pathology of disease caused by dengue virus and to developing vaccines for dengue and dengue hemorrhagic fever. The four types of dengue viruses and their mosquito vectors have spread widely during 1996-2000, especially in Latin America. Promising results have been seen in preliminary human testing of the candidate vaccine containing tetravalent, live, attenuated virus, developed in Thailand and licensed to Pasteur-Merieux-Connaught (France). Studies of the blood of infected volunteers demonstrated effective activation of T-cell immunity, as well as humoral immunity. Efforts to develop live virus vaccines based on chimeric flaviviruses are also continuing. Epidemiologic studies aiming to find a correlation between DNA sequence and severity of disease revealed a unique 3' noncoding region in a virus strain isolated from a patient with dengue shock syndrome. In another study, an investigator reported development of a mouse model simulating some of the manifestations of dengue hemorrhagic fever.

A vaccine derived from inactivated Japanese encephalitis (JE) virus from mouse brain has been in use for more than 40 years. The vaccine is licensed in Japan, the United States, and several South and Southeast Asian nations. It is effective but costly and is associated with toxic effects. During the last 5 years, research to develop an improved JE vaccine has been intensive. A DNA vaccine incorporating complementary DNA (cDNA) of the prM and E genes of JE virus was shown to protect mice. Chimeric candidate vaccines using live, attenuated dengue 4 virus or 17D yellow fever virus, with insertion of prM and E genes from JE virus, have shown great promise. The 17D-JE chimera has been tested in monkeys and is ready for clinical trials. In one study, use of suramin, an antiviral drug, in cell cultures infected with JE virus decreased the titer of JE virus and was not toxic to the cells. No drugs are effective in treatment of JE. The whereabouts of JE virus in the winter has long been a mystery. Experiments have now shown that JE nucleic acid was present in winter in pig blood in Kanazawa, Japan.

Significant progress has been made in the understanding of rotaviruses, Norwalk virus, caliciviruses, and astroviruses, all of which contribute to the morbidity and mortality of viral diarrhea. The first rotavirus vaccine was licensed in the United States in 1998. Toxic effects from the vaccine subsequently led to its withdrawal from the market in 1999, but such a vaccine has the potential to prevent many childhood deaths from diarrhea caused by rotavirus, especially in less developed nations. Other advances in control of rotavirus include discovery of antiviral agents from natural plant substances; development of systems for serotyping that can facilitate selection of viral strains for future vaccines; and elucidation of the intrafamilial spread of group C rotaviruses, mostly in adults.

In other studies, the complete genome sequence of Norwalk virus was determined. In one investigation, Norwalk virus caused 39% of winter diarrhea in Japan. A feline model for caliciviruses will be an important tool in future studies of these viruses. Modern technology, including reverse transcriptase-polymerase chain reaction and latex agglutination, have revolutionized the identification and typing of these agents that cause diarrheal disease. Aichi virus has now been sequenced and shown to be a new genus in the Picornaviridae family.

Rabies continues to be endemic in Asia, and raccoon rabies is spreading relentlessly in the northeastern United States. The rabies glycoprotein was shown to be the dominant protective factor, and DNA rabies G vaccine, jointly with DNA-expressing cytokines gave excellent protection in a mouse model. Intensive work to explore the ability of the rabies virus to regulate protein synthesis and transport in the cytoplasm continues. The M protein co-localizes with the G protein when they are co-expressed by the virus. Deletion of portions of the rabies virus showed that the M internal domain controlled its association with G protein. Due to a recent change in the epidemiology of

rabies as a cause of human deaths in the United States, the rabies genotype of the silver-haired bat now predominates. Because there is usually no history of a bat bite in persons who die from rabies, the possibility of aerosol exposure has been suggested.

In a highly significant finding, Hantavirus pulmonary syndrome was discovered in South America, and cases there now outnumber those in North America. Furthermore, in an epidemic in Argentina, investigators demonstrated person-to-person transmission, which is thought to be unique to the South American Hantaviruses. Other findings by the Panels include (1) development of recombinant diagnostic antigen for Hantavirus in baculoviruses; (2) high prevalence of both Seoul virus and Hantaviruses in China; and (3) evidence in the Americas, as already demonstrated in Asia, that Hantaviruses evolved with their rodent hosts.

In other developments, the Panels have fostered research on the basic replication mechanisms and structure of alphaviruses and have progressed in the use of replicons of Venezuelan equine encephalitis virus and Sindbis virus as efficient vectors of genes for vaccine delivery and, perhaps in the future, for delivery of other genes to arthropods or vertebrate animals. In addition, the complete sequence of Sagiyama virus was determined and an infectious clone is now available.

Since the discovery of tick-borne encephalitis virus in a patient in Hokkaido, Japan, early in the 1990s, studies indicate that the virus is endemic there, that the local Japanese strain is less virulent for mice than the Russian prototype strain, and that the vaccine for tick-borne encephalitis licensed in Europe produces neutralizing antibody against the Japanese virus.

Future Goals

Future goals will include efforts to stimulate U.S.-Japanese collaboration in virology in the United States, Japan, and the Pacific Basin. Particular emphasis will be on important new and emerging viruses in these regions.

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